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Reply

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

We thank Dr. Golwala and Dr. Spallarossa and colleagues for their interest in our study. Both ask about the lack of association found in our study (1) between troponin elevation and benefit from pharmacological intervention. The value of troponins to predict left ventricular systolic dysfunction (LVSD) has been reported with anthracyclines but not with other drugs (2). However, we do not believe that our results are contradictory to those of Cardinale et al. (3); differences in the patient population, intensity and type of chemotherapy, and protocol design of both studies may account for their different results. Cardinale et al. included only patients with positive troponin levels 1 month after treatment, selecting a population at a particularly high risk for developing a marked drop in left ventricular ejection fraction (LVEF) (43% in their control group), whereas we enrolled all incoming patients. In our study, 10 of the 11 patients with positive troponin levels had acute leukemia, a subgroup of patients that received anthracyclines and a more intense chemotherapy regimen and in whom we observed a marked effect of the intervention. Large randomized trials are needed to determine whether a strategy of primordial prevention with cardioprotective drugs to all patients is more effective than a troponin-directed strategy.

Dr. Golwala questions the value of the results of the intervention on a secondary endpoint of the study, the combined endpoint of mortality, heart failure, and significant LVSD, due to the potential confounding factor of sepsis. As discussed in the paper, because two-thirds of all deaths were related to sepsis, it is difficult to elucidate whether enalapril and carvedilol could have influenced mortality. However, survivors of sepsis had a lower LVEF, and this condition is a well-known determinant of mortality. Other factors should be considered because 8 of the 13 patients who survived a septic episode had acute leukemia, a subgroup of patients with a marked benefit from the intervention. In addition, the effects on LVEF were observed, not only among the patients who survived a septic episode, but also in the other 66 patients, especially in patients with acute leukemia in which a $-5 \pm 5.7\%$ intergroup absolute difference was observed. Finally, a positive trend for the intervention was also observed in the number of patients with heart failure or a drop of $\geq$10% in LVEF, although the incidence was too low to preclude definite conclusions.

We agree with Dr. Spallarossa and colleagues that the antioxidant effect of carvedilol may play an important role in its cardioprotective effect (as do their demonstrated antiapoptotic and pleiotropic effects) and on the importance to correctly treat hypertensive patients treated with chemotherapy. Because, by protocol, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers were not allowed in our study, the 8 hypertensive patients of the control group were treated with amlodipine; at 6 months follow-up, their mean systolic pressure was 122 ± 13 mm Hg.

Finally, we understand the safety concern of Dr. Spallarossa et al. about the rapid initial up-titration of enalapril and carvedilol in these high-risk patients. This concern was indeed the reason for not performing a double-blind study with placebo. The protocol used was safe because all patients had normal LVEF and were treated in-hospital during frontline therapy under close supervision for a mean of 1 month, and in no cases did the study treatment prevent the patients from receiving the optimal chemotherapy regimen. The tight cooperation we had between hematologists and cardiologists was certainly the key.

***Xavier Bosch, MD**
Marta Sitges, MD
Montserrat Rovira, MD
José Tomás Ortiz-Pérez, MD
Jordi Esteve, MD

*Hospital Clinic
Servicio de Cardiología
Villarroel 170
08036 Barcelona, Catalonia
Spain
E-mail: xbosch@clinic.ub.es

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